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<p>(21) International Application Number: PCT/GB98/00658 (22) International Filing Date: 3 March 1998 (03.03.98) (30) Priority Data: 9704370.7 3 March 1997 (03.03.97) GB (71) Applicant: DARWIN DISCOVERY LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). (72) Inventor: GENNERY, Brian, Albert; Darwin Discovery Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). (74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: USE OF LEVOBUPIVACAINE IN COMBINATION WITH OPIOIDS OR ALFA2-AGONISTS FOR PROVIDING ANAESTHESIA OR ANALGESIA</p> <p>(57) Abstract</p> <p>A method of providing anaesthesia or analgesia in a human patient, comprising the simultaneous, separate or sequential administration of levobupivacaine and also another drug selected from the group consisting of opioids and $\alpha 2$-agonists.</p>		

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USE OF LEVOBUPIVACAINE IN COMBINATION WITH OPIOIDS OR ALFA2-AGONISTS FOR PROVIDING ANAESTHESIA OR ANALGESIA

Field of the Invention

This invention relates to a new formulation and a new use for levobupivacaine
5 or (S)-1-butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide.

Background of the Invention

Racemic bupivacaine is an effective long-acting local anaesthetic, and may be given as an epidural. However, racemic bupivacaine is cardiotoxic, having depressant electrophysiological and mechanical effects on the heart. It should therefore be used
10 with caution in cardiac-compromised patients, and the use of high doses and high concentrations is contraindicated.

In particular, bupivacaine has produced death in a number of patients, including women in childbirth and when used in the Bier's block technique. Although the incidence of death has been relatively small, the concern has been sufficient to stop the use of
15 0.75% bupivacaine for obstetrics and the proscribing of bupivacaine for use in Bier's blocks.

In addition, due to its mode of action, directly on the nervous system, at higher doses, bupivacaine is known to have undesirable central nervous system (CNS) side-effects which, *prima facie*, are connected to its anaesthetic activity. Indeed, the
20 occurrence of CNS side-effects is one of the major factors limiting the use of this drug in normal clinical practice employing techniques such as local infiltration, nerve block, field block, epidural and spinal blocks.

It has been suggested that levobupivacaine is less cardiotoxic than dextrobupivacaine and racemic bupivacaine. See, for example, Vanhoutte *et al*, Br. J. Pharmacol. 103:1275-1281 (1991), and Denson *et al*, Regional Anaesthesia, 17:311-316
25 (1992). However, these reports are based on work *in vitro*, and cannot necessarily be extrapolated to any mammals, and certainly not to humans.

The surprising and effective utility of levobupivacaine in man, *in vivo*, is evidenced for the first time in WO-A-9510276, WO-A-9510277 and Gristwood *et al*,
30 Exp. Opin. Invest. Drugs 3(11):1209-12 (1994).

Summary of the Invention

This invention is based on the surprising discovery that levobupivacaine is an effective and especially safe anaesthetic, in combination with another drug, i.e. an opioid or $\alpha 2$ -agonist, e.g. an agent selected from morphine, fentanyl and clonidine. Synergy between these drugs allows for the amount of either or each to be reduced, e.g. below conventional dosing.

Description of the Invention

In the method of the present invention, levobupivacaine may be provided in solution, for infusion or injection into the epidural or spinal space, or for administration by any of the conventional means for obtaining a nerve or field block. In addition to the anaesthetic blocks conventionally provided by the racemate, levobupivacaine may also be useful in providing blocks in areas of the body where the risk of systemic exposure to the drug, and therefore CNS side-effects, is particularly high. Examples include open wounds and vascular areas, for instance using intercostal blocks for the latter.

For upper limb surgery at least, infusion into the body near the base of the limb may be appropriate. A regional or plexus block may also be used.

Administration of levobupivacaine may be continuous or bolus administration. This may be done using conventional apparatus, e.g. including means for the patient to induce infusion as desired. The daily dose administered to the patient may be in the relatively low range known for the administration of racemic bupivacaine, but, because of the decreased CNS side-effects of levobupivacaine, may be higher than the conventional dose for the racemic drug. The total dose of levobupivacaine may be around, or in excess of, 2 mg per kg of patient body weight.

The concentration of levobupivacaine to be given can be that conventionally used for the racemic drug, e.g. from 0.25% w/v and typically about 0.5% w/v. However, the amounts of levobupivacaine and of the other drug can each be lower than they would be if administered independently. True synergy may be seen. Thus, for example, the dosage of fentanyl or morphine can be halved, and 0.125% or 0.0625% w/v levobupivacaine can be used. The solution of levobupivacaine is preferably aqueous.

The solution may typically be put up in unit doses of from 1 to 15 ml, and preferably of around 10 ml. However, the unit doses may be higher, for instance up to

40 ml or higher. The unit doses may be in the form of ampoules, which may be made of any suitable material, e.g. glass or an appropriately impervious plastics material. Unit dosages comprising at least 75 mg, but preferably less than 200 mg, of levobupivacaine can be administered, and more preferably the unit dosage is in the range 80 to 150 mg.

5 The administration of levobupivacaine over a range of concentrations, including those currently used for the racemic drug and the higher concentrations described above, can be carried out for significantly longer periods than at present, again as a result of the reduced CNS side-effects experienced with levobupivacaine. For instance, levobupivacaine can be administered to a patient safely for at least 24 hours, often up to
10 72 hours, and even for periods of up to a week or a fortnight, or longer. It can, of course, be administered for similar periods already used for the racemic drug, e.g. between 3 and 6 hours. Levobupivacaine may be particularly valuable for the maintenance of post-operative analgesia, e.g. over the period 8-24 hours after surgery.

15 The method of the present invention is particularly useful in surgical procedures carried out on patients who merely require surgery, and are otherwise healthy. The patient may also be cardiac or CNS-compromised, or predisposed to cardiac or CNS-related conditions, i.e. having a low CNS threshold.

20 For the purposes of this specification, the levobupivacaine is substantially free of dextrobupivacaine, i.e. preferably in at least 90%, and most preferably at least 99%, enantiomeric excess. Throughout this specification, reference to bupivacaine and its enantiomers includes pharmaceutically-acceptable salts thereof.

25 The other drug that is used in the invention may be formulated together with, or independently from, the levobupivacaine. It may be formulated in a manner that is already known for that drug. The drugs may be administered sequentially or simultaneously, according to need. In one preferred embodiment, a mixture, e.g. a solution, of both drugs is administered.

30 The other drug is chosen for its ability to complement the utility of levobupivacaine, especially in post-operative pain control. Examples of such other drugs are opioids and $\alpha 2$ -agonists such as morphine, clonidine, fentanyl, alfentanil, remifentanyl, diamorphine and dexmedetomidate.

The utility of the combination may be in any of the uses already described for levobupivacaine. See also the other Applications also filed 3rd March 1998, in the same name.

- The following Studies 1 to 3 illustrate the utility of the invention. An additional benefit of the invention is demonstrated by an eeg study in human subjects, wherein racemic bupivacaine was found to have a greater excitatory effect on the CNS than levobupivacaine.

Study 1

- Title:** Double-Blind Randomised Controlled Trial to Assess the Efficacy of 0.25% Levobupivacaine Combined with 0.005% Morphine, 0.25% Levobupivacaine Alone, or 0.005% Morphine Alone for Post-Operative Pain in Patients Undergoing Major Abdominal Surgery

- Design:** A randomised, double-blind, three arm, parallel-group, multicentre study. Patients were randomised to receive either levobupivacaine and morphine, or levobupivacaine alone, or morphine alone using a 1:1:1 patient allocation. A total of 68 patients were randomised into the study.

Dosage: 0.75% levobupivacaine as pre-operative anaesthetic to initiate block for surgery.

Randomised Study Medication for post-operative analgesic:

- | | |
|--------|---|
| 0.25% | levobupivacaine |
| 0.25% | levobupivacaine/0.005% morphine combination |
| 0.005% | morphine |

- Efficacy:** The median time to first verbal request for rescue, the primary efficacy study endpoint, was approx. 3 times shorter (8 h) for the combination than the time (24 h) for single drug. Fewer patients in the combination arm than in the morphine alone arm requested any rescue analgesia. Compared to patients in the morphine treatment group, significantly fewer patients in the combination arm requested ketorolac.

- Safety:** The 0.25% levobupivacaine/0.005% morphine combination was generally well tolerated and was associated with fewer study drug related adverse events than levobupivacaine or morphine alone. Cardiovascular adverse events reported were primarily reports of hypotension with similar incidence across treatment arms. None of

the seven serious adverse events reported was considered by the investigators to have a possible, or greater, causal relationship to study drug. There was significantly fewer premature withdrawals from the study due to adverse events in the combination treatment group compared to the levobupivacaine and morphine treatment groups.

- 5 **Conclusion:** Taken together, the results as a whole support the conclusion that compared to the individually administered agents in this trial, the combination of 0.25% levobupivacaine and 0.005% morphine has a clinically beneficial effect for use as post-operative analgesia in patients undergoing major abdominal surgery.

Study 2

- 10 **Title:** A Study to Assess the Efficacy and Safety of 0.125% Levobupivacaine, 0.125% Levobupivacaine plus 50 $\mu\text{g}\cdot\text{h}^{-1}$ Clonidine and 50 $\mu\text{g}\cdot\text{h}^{-1}$ Clonidine Alone Administered as a Continuous Extradural Infusion for Post-Operative Pain in Patients Undergoing Elective Hip Replacement Surgery

- Design:** Single centre, randomised, double-blind, three-limb parallel group study. 98
15 patients were recruited, of which 90 were evaluable for the efficacy analysis. The main criteria for inclusion were male and female patients aged between 18 and 80 years, weight within 50-110 kg, undergoing elective primary, unilateral replacement of hip joint.
Dosage: 3 x 5 ml injections of 0.75% levobupivacaine were given over 15 min, followed by up to 5 x 1 ml bolus injection of 0.75% levobupivacaine as required over a period of
20 5 min, until adequate block achieved. Three hours later, a continuous infusion was given over 24 h.

Clonidine was administered as a continuous infusion at a concentration of 50 $\mu\text{g}\cdot\text{h}^{-1}$ or in combination with 0.125% levobupivacaine, also at a concentration of 50 $\mu\text{g}\cdot\text{h}^{-1}$ given over 24 h.

- 25 **Efficacy:** For the primary efficacy variable, i.e. the total dose of morphine administered, the greatest difference was seen between the levobupivacaine treatment group and the levobupivacaine plus clonidine group (the levobupivacaine alone group requested a median of 23 mg more), with a p-value of <0.001. An analysis using the per-protocol population confirmed this assessment.

- 30 In addition, the time to first request for analgesia and the number of requests were seen to be significantly different between the treatment groups. The median times

to first request were 2.85 h, 12.49 h and 5.88 h in the levobupivacaine, levobupivacaine plus clonidine and clonidine treatment groups respectively.

Safety: No formal statistical analysis was performed on the safety data, however there was no great difference between the adverse events recorded in each group. The most

- 5 common event was hypotension.

Conclusion: Efficacy analysis suggests that the total dose of rescue medication is lower, the time until first request is longer, and the number of requests is reduced, in patients receiving levobupivacaine plus clonidine compared to patients receiving either agent alone. The combination shows an effect greater than additive.

10 **Study 3**

Title: Double-Blind, Randomised, Controlled Trial to Assess the Efficacy of 0.125% Levobupivacaine Combined with Fentanyl, 0.125% Levobupivacaine Alone, or Fentanyl Alone Using Patient-Controlled Epidural Anaesthesia for Post-Operative Analgesia in Patients Undergoing Major Orthopaedic Surgery

- 15 **Design:** A randomised, double-blind, three-arm, parallel-group multicentre study. Patients were randomised to receive either the combination of levobupivacaine and fentanyl, levobupivacaine alone, or fentanyl alone using a 1:1:1 patient allocation.

A total of 68 patients were enrolled into this study from two study sites. 28 patients discontinued prior to the end of the 24-hour post-operative study period and 40

20 completed the study.

Dosage: 0.75% levobupivacaine as pre-operative anaesthetic to initiate block for surgery.

Randomised Study Medication:

- | | | |
|----|---------|---|
| 25 | 0.125% | levobupivacaine |
| | 4 µg/mL | fentanyl |
| | 0.125% | levobupivacaine combined with 4 mcg/mL fentanyl |

Efficacy: The primary measure of efficacy, the time to first request for administration of PCEA following surgery, was significantly longer in the levobupivacaine/fentanyl combination treatment group compared to the fentanyl treatment group ($p = 0.007$).

- 30 Pain assessments indicated significantly less discomfort at the 6-hour ($p = 0.022$) and 12-hour ($p = 0.002$) post-operative time points for the patients in the combination treatment

group, compared to patients in the fentanyl treatment group. Overall, patients receiving the levobupivacaine and fentanyl combination reported less pain than the patients receiving fentanyl alone. This was corroborated by the investigator's global assessment.

Safety: The combination was generally well tolerated. Cardiovascular adverse events

- 5 reported were primarily reports of hypotension with similar incidence across treatment groups. None of the six serious adverse events reported by patients receiving study drug was considered by the investigators to be related to study drug. In total, 17 patients (26%) withdrew from the study prematurely due to inadequate pain control, with a higher incidence in the single therapy arms compared with combination.

- 10 **Conclusion:** The results of this study demonstrate a significant additive effect of a combination of 0.125% levobupivacaine with 4 µg/mL fentanyl over 4 µg/mL fentanyl alone as an analgesic for use after orthopaedic surgery. This enhanced efficacy was not associated with an increased risk or severity in adverse events. In particular, the nausea/vomiting associated with the use of fentanyl was reduced using the combination.

CLAIMS

1. Use of levobupivacaine and also another drug selected from opioids and α 2-agonists for the manufacture of a medicament for providing anaesthesia or analgesia in a human patient.
2. Use according to claim 1, wherein the amounts of levobupivacaine and of said another drug that are administered are each reduced relative to the dose that would otherwise be given for either.
3. Use according to claim 1 or claim 2, for providing post-operative analgesia.
4. Use according to any preceding claim, wherein the levobupivacaine and the another drug are administered by continuous infusion.
5. Use according to any of claims 1 to 4, wherein said another drug is morphine.
6. Use according to any of claims 1 to 4, wherein said another drug is fentanyl.
7. Use according to any of claims 1 to 4, wherein said another drug is clonidine.
8. A product comprising levobupivacaine and another drug selected from opioids and α 2-agonists, as a combined preparation for simultaneous, separate or sequential use in providing anaesthesia or analgesia.
9. A product according to claim 8, comprising a sterile solution of levobupivacaine and said another drug.
10. A product according to claim 8, which comprises a sterile aqueous solution containing less than 0.5% levobupivacaine.
11. A product according to any of claims 8 to 10, wherein said another drug is morphine.
12. A product according to any of claims 8 to 10, wherein said another drug is fentanyl.
13. A product according to any of claims 8 to 10, wherein said another drug is clonidine.

INTERNATIONAL SEARCH REPORT

In .ational Application No

PCT/GB 98/00658

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/445 A61K31/485 A61K31/415 //(A61K31/445,31:445),
(A61K31/445,31:415),(A61K31/485,31:445)

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	---	5-7, 11-13
X	WO 95 10276 A (CHIROSCIENCE LTD ;BARDSEY HAZEL JUDITH (GB); MATHER LAURENCE (AU)) 20 April 1995	1-4,8-10
Y	see page 3, line 21-23; claim 4 ---	5-7, 11-13
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Authorized officer

Herrera, S

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GRISTWOOD R ET AL: "REDUCED CARDIOTOXICITY OF LEVOBUPIVACAINE COMPARED WITH RACEMIC BUPIVACAINE (MARCAINE): NEW CLINICAL EVIDENCE" EXPERT OPINION ON INVESTIGATIONAL DRUGS, vol. 3, no. 11, November 1994, pages 1209-1212, XP000610836 see page 1211, right-hand column, last paragraph ---	1-13
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In: International Application No

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